Effect of beta₁ selective adrenoceptor blockade on physiological response to exercise

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SUMMARY The effect of the beta₁ selective adrenoceptor blocker, atenolol, on the physiological response to exercise was studied in 12 healthy young men. Oral atenolol (100 mg) and placebo were administered in a randomised double blind crossover fashion an hour and a half before an intermittent multistage cycle ergometer exercise test. At maximal effort oxygen consumption, pulmonary ventilation, carbon dioxide output, and respiratory exchange ratio were not modified by atenolol. In contrast, maximal heart rate and performance time were significantly reduced after atenolol. Nevertheless, because the relation of percentage of maximal oxygen consumption to percentage of maximal heart rate was not changed by atenolol both the absolute and relative oxygen consumption corresponding to 70% and 85% of the maximal heart rate remained unaltered.

These data suggest that recommendations of exercise intensity may be determined on the basis of a calculated percentage of the predetermined maximal heart rate in persons without symptomatic coronary heart disease receiving beta₁ selective adrenoceptor blockers.

Beta adrenoceptor blocking drugs constitute a major advance in cardiovascular therapeutics. Their clinical use in appropriately selected patients with hypertension and angina pectoris is well established.^{1,2} Furthermore, recent data indicate that treatment with beta adrenoceptor blockers can reduce mortality in the early years after myocardial infarction.³ Exercise conditioning has emerged as an important therapeutic factor in the management of these same diseases.^{4,5} Nevertheless, despite the now common practice of prescribing a programme of formal exercise training for patients receiving beta adrenoceptor blockers limited information is available concerning the possible influence of these agents on the currently accepted principles of exercise intensity prescription. In fact, a review of published reports shows only two substantial studies,^{6,7} both of which require further amplification to delineate the precise effect of beta adrenoceptor blockade on the physiological response to exercise. Moreover, although recent research findings suggest an advantage for the use of beta₁

selective adrenoceptor blockers in patients receiving beta adrenoceptor blockade treatment who participate in endurance exercise,^{8,9} the two earlier studies investigated non-selective beta adrenoceptor blockade alone.

To clarify the situation further we examined the effect of the beta₁ selective adrenoceptor blocker, atenolol, on exercise physiology in 12 healthy young men.

Subjects and methods

Twelve healthy, young adult male Caucasians served as subjects. All were volunteers, and informed consent was obtained before the study. The physical characteristics of the subjects included: age 21 (1.2) years (mean (standard deviation)); height 176 (5) cm; body weight 76.26 (6.5) kg; and body fat 14.1 (2.1)%. Each subject gave a clinical history and underwent physical examination, resting and maximal dynamic exercise electrocardiography, pulmonary function tests, serum electrolytes, blood urea nitrogen, and fasting blood glucose measurements, liver function tests, and full blood count, all of which were normal. None of the subjects was taking medication.

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Accepted for publication 29 January 1985

The trial was conducted in a randomised double blind crossover fashion. Each subject received atenolol (tenormin 100 mg) or placebo as a single oral dose an hour and a half before upright exercise performed on a calibrated cycle ergometer (Monark). The selection of a single oral dose was based on the observation that a significant difference was not evident in healthy subjects for submaximal or maximal exercise performance in response to beta adrenoceptor blockers given as a single dose or as twice daily doses for four weeks.¹⁰ Tests were conducted in a controlled environment with a temperature of 20°C dry bulb and relative humidity of 55% and were held at least one week apart.

All subjects were given an initial familiarisation trial. On study days meals, tea, coffee, cola beverages, and cigarettes were avoided for at least three hours before exercise. Before exercise subjects rested for one hour in a comfortable environment. After a four minute warm up at 60 W, the subjects participated in a discontinuous graded exercise test. Subjects started cycling at a work rate of 90 W, the pedal frequency being 60 rpm. The pedal frequency remained constant and the workload was increased by 30 W with each successive three minute exercise period until the pedal frequency could not be maintained. Subjects rested for three minutes between exercise periods. Since initial workload was the same with placebo and atenolol treatment performance time could be measured. Ventilatory variables were measured over the final minute of each work period. Subjects exhaled through a Hans Rudolph valve into meteorological balloons. The expired gas volume was determined in a Warren E Collins chain compensated spirometer, and the oxygen and carbon dioxide contents determined on a portion of the expired gas volume. The gas concentrations were measured with an Applied Electrochemistry S-3A oxygen analyser and a Gould Godart Capnograph Mark II carbon dioxide analyser. Heart rate was calculated from electrocardiograms (CM5 placement) obtained during the final 15 seconds of each workload using a Hellige Multiscriptor EK-33 electrocardiograph, the chart rate being 25 mm/s. Peak heart rate and oxygen consumption attained during exercise were taken as maximal heart rate and

maximal oxygen consumption respectively. Individual and group regression equations relating the percentage of maximal oxygen consumption to the percentage of maximal heart rate were calculated, using standard linear regression analysis, with and without beta adrenoceptor blockade. The percentage of the maximal oxygen consumption and the absolute oxygen consumption were determined from the derived individual regression equations for 70% and 85% of the maximal heart rate with and without atenolol treatment.

The significance of differences between experimental variables was analysed using a paired *t* test. Statistical significance was established at the 0.05 confidence level.

Results

Table 1 shows the effect of atenolol on cardiorespiratory variables at maximal exercise and exercise performance. Maximal oxygen consumption, pulmonary ventilation, carbon dioxide output, and respiratory exchange ratio were not significantly altered by beta adrenoceptor blockade. Maximal heart rate was, however, reduced by 23.1% ($p < 0.001$) and cycle ergometer performance time by 4.2% ($p < 0.05$) after treatment with atenolol.

Despite the considerable negative chronotropic effect of atenolol during exercise, the relation of percentage of maximal oxygen consumption to percentage of maximal heart rate was not modified (Figure) during beta adrenoceptor blockade in the present study. Likewise, both the relative and absolute oxygen consumptions for 70% and 85% of the maximal heart rate were unaltered by atenolol (Table 2).

Discussion

Whereas some researchers have reported a decrease in maximal oxygen consumption after beta adrenoceptor blockade,¹¹⁻¹³ others have not found such an effect.¹⁴⁻¹⁶ Recently, Tesch and Kaiser attributed this inconsistency to differences in test subject selection, and their findings with the non-selective beta adrenoceptor blocker propranolol indicated that a

Table 1 Effect of atenolol during maximal exercise on cardiorespiratory variables and exercise performance. Figures are mean (SD) values ($n=12$)

	Placebo	Atenolol	% Change
Maximal oxygen consumption (l/min)	3.43 (0.37)	3.36 (0.36)	2
Pulmonary ventilation (l/min)	104.0 (12.9)	103.7 (12.9)	0.3
Carbon dioxide production (l/min)	3.87 (0.48)	3.85 (0.49)	0.5
Respiratory exchange ratio	1.14 (0.04)	1.15 (0.05)	0.9
Heart rate (beats/min)	199 (7)	153 (11)	23.1*
Performance time (min)	20.25 (3.07)	19.4 (2.41)	4.2†

* $p < 0.001$; † $p < 0.05$.

Figure Effect of atenolol on the relation of percentage of maximal oxygen consumption to percentage of maximal heart rate in 12 healthy subjects. Regression lines together with 95% confidence limits are shown for placebo (solid lines) and atenolol (broken lines). The equations for the regression lines are: placebo— $y = 1.32x - 36$ ($r = 0.95$); atenolol— $y = 1.40x - 42$ ($r = 0.95$), where y is the percentage of maximal oxygen consumption and x the percentage of maximal heart rate.

significant reduction in maximal oxygen consumption could be expected in physically active men after pharmacological blockade of beta adrenoceptors.¹¹ In the present study, however, maximal oxygen consumption was essentially unaltered by atenolol. We suggest that this seemingly conflicting observation can be ascribed to differences between beta₁ selective and non-selective beta adrenoceptor blockade⁹ and to our use of an intermittent test protocol. Regarding the latter, the fatiguing effect of beta adrenoceptor blockade^{8,9} might prevent subjects from attaining their true maximal oxygen consumption during exercise testing, a response which is likely to be lessened by the use of an intermittent as opposed to continuous test protocol.

At present it is widely accepted that endurance conditioning performed at 70% to 85% of the predetermined maximal heart rate will yield the exercise intensity needed for the stimulation of a physiological training effect.^{6,17,18} Our study shows that, although the reduction in maximal heart rate is considerable during beta adrenoceptor blockade, atenolol does not alter the relation of percentage of maximal oxygen consumption to percentage of maximal heart rate in healthy subjects. Furthermore, because the maximal oxygen consumption was not reduced by atenolol in our study the absolute as well as the relative oxygen consumption corresponding to 70% and 85% of the maximal heart rate were not significantly modified. Thus, although our finding cannot be extrapolated to patients with coronary heart disease whose exercise is limited by angina pectoris, the present data suggest that exercise intensity may be determined by using a calculated percentage of the predetermined maximal heart rate and should yield the expected relative and absolute exercise intensity in physically active patients with hypertension or asymptomatic coronary heart disease treated with beta₁ selective adrenoceptor blockers. In addition, since beta adrenoceptor blockade appears to exert its greatest effect on the cardiorespiratory response to exercise in young physiologically active subjects¹¹ the present finding is also likely to be applicable to older less active patients.

Previously, Hossack *et al* and Pollock and Foster investigated the effect of propranolol on exercise training programmes in subjects with⁶ and without⁷ coronary heart disease respectively. Both groups reached a similar conclusion to that of the present study regarding relative exercise intensity prescription, but no data were presented for the absolute oxygen consumption corresponding to a specific heart rate range. Although a note of caution is appropriate concerning a further interpretation of their findings, it does appear on analysis of their results^{6,7,19} that during propranolol treatment the absolute exercise intensity for a given percentage of the maximal heart rate is, in contrast to our findings with atenolol in healthy subjects, essentially unchanged or increased in

Table 2 Effect of atenolol on absolute and relative oxygen consumption for 70% and 85% maximal heart rate. Figures are mean (SD) values ($n = 12$)

	Placebo	Atenolol	% Change
70% maximal heart rate:			
Heart rate (beats/min)	139 (5)	107 (8)	23*
Oxygen consumption (l/min)	1.86 (0.35)	1.79 (0.38)	3.8
% maximal oxygen consumption	53.9 (6.5)	53.0 (7.5)	1.7
85% maximal heart rate:			
Heart rate (beats/min)	169 (6)	130 (10)	23.1*
Oxygen consumption (l/min)	2.59 (0.36)	2.59 (0.39)	0
% maximal oxygen consumption	75.3 (4.5)	77.0 (5)	2.3

* $p < 0.001$.

patients with coronary heart disease (depending on the precise cardiac status) and decreased in healthy subjects. This observation may be of clinical as well as scientific importance. The interaction of exercise conditioning and beta adrenoceptor blockade is presently controversial in that patients with coronary heart disease seem capable of deriving a pronounced training effect,²⁰⁻²² whereas the training effect appears to be significantly attenuated with non-selective but not beta₁ selective beta adrenoceptor blockade in healthy subjects.²³ While it is commonly believed that the magnitude of the physiological adaptation to exercise training is dependent on the relative rather than the absolute exercise intensity,¹⁷ this might not be entirely true for a given subject with and without beta adrenoceptor blockade. We speculate that the different training responses in subjects receiving beta₁ selective and non-selective beta adrenoceptor blockers and with a different cardiac status might be partly related to the differing effect of these variables on the absolute exercise intensity corresponding to a specific percentage of the maximal heart rate.

This study was supported by grants from ICI (South Africa) and Execucare Preventive Fitness Maintenance.

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